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Award Number: DAMD17-00-1-0523

TITLE: Genetic Susceptibility to Prostate Cancer in the Netherlands

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REPORT DATE: August 2002

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 2002	Annual (1 Aug 01 - 31 Jul 02)

4. TITLE AND SUBTITLE
Genetic Susceptibility to Prostate Cancer in the Netherlands

5. FUNDING NUMBERS
DAMD17-00-1-0523

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

Studies of the genetics of populations that were historically endogamous for reasons of geography, religion, or language have contributed substantially to our understanding about hereditary predisposition to cancer. One such population is found in the Netherlands where multiple, prevalent, population-specific founder mutations have been identified. Genetic susceptibility to prostate cancer is being investigated in the Netherlands Cohorts Study (NLCS) on Diet and Cancer, which has identified over 800 cases of prostate cancer among 58,279 male participants. From this study, we have identified 300 cases and 300 controls from among men of comparable age to identify markers near prostate cancer susceptibility genes that are present at higher frequency in the group of men with prostate cancer. We have optimized the methods for analysis of these markers. During the next year, we will apply these methods to analyzing the samples that have been collected.

14. SUBJECT TERMS
prostate cancer, linkage disequilibrium, association

15. NUMBER OF PAGES
49

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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INTRODUCTION

This study uses several observations about the genetic basis of prostate cancer to enhance the efficiency of identifying susceptibility genes. 1) Prostate cancer is a multi-step genetic disorder in which some of the observed genetic alterations in prostate cancer cells were acquired through the germline. 2) The chromosomal locations of some of these genes can be identified readily in prostate cancer cells on the basis of their demonstrating loss of heterozygosity. 3) Historically, certain populations have been endogamous causing them to have more genetic homogeneity and to have prevalent founder mutations in some of their disease susceptibility genes. As a result of the population's endogamy, short chromosomal regions have remained identical by descent, leading to recognizable associations of the founder mutations with linked marker alleles (*linkage disequilibrium*). The Dutch represent such a population.

BODY

Task 1. Subject identification. Months 12-24

The project started six months late because of delays in contract negotiation and subsequently by the terrorist events in New York City of 11 September 2001. Since that time, individuals with prostate cancer have been identified using the Pathology and Cancer Registry database in the Netherlands. The medical histories of each of these subjects have been reviewed, confirming diagnosis of prostate cancer, and noting age and Gleason score at time of diagnosis. Currently, for each subject, tissue blocks are being obtained from non-cancerous tissues (usually lymph nodes) and thick (50 micron) sections are being cut. DNA is being purified from these sections using a protocol optimized in our laboratory and then quantified. To extend the utility of these sections, a technique for whole genome amplification using primer extension preamplification (PEP) was optimized. This technique reproducibly provides approximately 50-fold amplification of the DNA samples. This technique is being applied. Buccal swab samples have been collected from the whole subcohort of the Netherlands Cohort Study on Diet and Cancer and DNA has been extracted from these samples. From these samples, 300 will be selected for subsequent analysis. To date, we have collected buccal swabs from 940 male controls from the subcohort of the Netherlands cohort study. We have identified 641 cases of prostate cancer and have collected normal tissue samples for DNA extraction from 274 cases. This represents collection of approximately 2/3 of the cases.

Task 2. Development of markers. Months 12-24

A. Markers from regions associated with loss of heterozygosity (LOH) in prostate cancer will be identified and fluorochrome-labeled primers will be synthesized. We have identified microsatellite markers for each of the following chromosomal regions 1q24-q25, 7q31, 8p21-p22, 10q23-q25, 13q14, 16q22, 17p, 17q21-q22, Xq11-q13. Because of uncertainties about relative map positions, we have confined our markers to those which have shown (LOH) in a high proportion of subjects in a single report, to those which show (LOH) in more than one report, or to those whose map positions are known with a high degree of confidence from the GeneMap99 (http://www.ncbi.nlm.nih.gov/GeneMap99) and which are tightly linked to markers that show LOH. In addition, we have added markers for the following chromosomal regions that have shown linkage to prostate cancer susceptibility in families with multiple affected

members, 1q24-25, 1q42-43, and Xq27-28 (Smith, et al., 1996, Cooney, et al., 1996, Gronberg, et al., 1997, Xu, et al., 1998, Berthon, et al., 1998).

B. Standard PCR conditions will be developed for each of these markers. The primer sequences for each of these markers was identified using standard databases (http://www.gdb.org). The predicted sizes of the PCR product alleles were noted and markers yielding products of different predicted sizes were grouped and labeled with one of three different fluorescent dyes (tet, fam, hex). The net effect of this grouping is that multiple markers can either be amplified simultaneous and/or pooled from separate amplifications to minimize the number of electrophoretic runs. Procedures for pooling separate amplification reactions have been optimized.

Different thermostable enzymes were tested for their fidelity for amplifying microsatellites, including AmpliTaq, AmpliTaq Gold, Platinum Taq, Platinum Tsp, and Expand High Fidelity. Among these enzymes, Platinum Tsp (Life Technologies, Gaithersburg, MD) was found to produce the most reliable amplification with the least stutter and the least random addition of an adenine at the 3' end of the PCR product. For each of the markers, different PCR conditions were tested, varying temperature and magnesium chloride concentrations, and the optimum conditions were defined.

KEY RESEARCH ACCOMPLISHMENTS

Development of DNA databases from cases and controls for genomic analysis.

Development of high-quality, reproducible methods for microsatellite typing

Development of high-quality, reproducible methods for whole genome amplification

REPORTABLE OUTCOMES

Proposal, "Mentorship Program in Prostate Cancer Genetics" K24 (CA85326-01A1), was funded by the National Cancer Institute.

Manuscripts

Zeegers MPA, Jellema A, Houwing J, Ostrer H. Empiric risks of prostate cancer for relatives of prostate cancer patients. JAMA, submitted.

Nieder AM, Taneja SS, Zeegers MPA, Ostrer H. Genetic counseling for prostate cancer risk. Clinical Genetics, submitted.

CONCLUSIONS

This works demonstrates the feasibility for high-throughput multiplex microsatellite marker analysis and the feasibility for extending small samples of DNA 50-fold for genetic analysis. It creates the foundations for the analyses that will be performed in the remainder of this study.

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Running title

Empiric risk of prostate cancer for relatives of a prostate cancer patient.

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Word Count: Abstract (250), Text (3058)

Abstract

BACKGROUND. Although narrative reviews have concluded that there is strong support for familial clustering of prostate cancer, the association has never been quantified systematically in reviews. The purpose of this meta-analysis was to summarize and quantify the recurrence risk ratio with emphasis on the degree of relatedness, the relationship of the family member, the number of affected family members and the age at diagnosis.

METHODS. The authors included 32 population-based studies and calculated summary recurrence risk ratios ($S\lambda$) by random effects meta-regression analyses. They also evaluated changes in summary estimates according to differences in study methodology.

FINDINGS. $S\lambda$ was 2.46 (95% 2.14 – 2.82) for first-degree family members. The $S\lambda$ appeared to be higher for men with an affected brother (3.28, 95%CI: 2.84-3.78) than for men with an affected father (2.18, 95%CI: 1.89-2.51). Whereas the recurrence risk ratio for men with second-degree relatives with prostate cancer was only slightly elevated (1.68, 95%CI: 1.07-2.64). The nature of this familial clustering is such that $S\lambda$ rises with decreasing age of the patient and family members, with increasing genetic relatedness of the affected relative and with an increase in the number of individuals affected within the family. No significant differences were observed in studies that analysed familial recurrence risks based on ethnicity.

INTERPRETATION. These studies demonstrate consistently that family history is a significant risk factor for developing prostate cancer. This meta analysis provides precise quantitative estimates that can be used for providing genetic counselling to the male family members of men with prostate cancer.

Keywords: Prostate cancer, Family history, (Genetic) Epidemiology, Meta-analysis, Genetic Counselling

Introduction

Prostate cancer is regarded as one of the most common cancers in the Western World. Presently, in the United States this disease is the most commonly diagnosed malignancy among men. The incidence is increasing by 10%-20% every 5 years, even when screen-detected cancers are disregarded[1]. Although the incidence of latent prostate cancer appears to be constant throughout the world, the incidence of clinical forms varies substantially[2]. African-American men have long been known to have the highest rates of prostate cancer in the world, whereas native Japanese and Chinese men (and probably other Asian populations such as Koreans) have lowest known prostate cancer rates[3]. This difference has been explained by both environmental and genetic influences.

Although prostate cancer is not widely recognised as a familial cancer, there is substantial evidence that it does indeed cluster in families. Attempts to elucidate the familial nature of prostate cancer began approximately 45 years ago after one study showed a higher incidence of prostate cancer in close relatives of patients with prostate cancer than in those of control patients[4]. Further population-based studies confirmed this familial clustering of prostate cancer[5-36], although the magnitude of the estimated risk varied.

To our knowledge, no meta-analysis of all previous studies on familial clustering of prostate cancer has been conducted so far. Earlier narrative reviews on family history and prostate cancer have summarized the association for first-degree familial clustering of prostate cancer by estimating a general relative risk without calculation or systematic collection of data[24,37-44]. According to these narrative reviews, men with first-degree family members with prostate cancer have two to four times the risk of men with no relatives with this disease. The magnitude of the other aspects of familial clustering (e.g., type of family member, number of affected family members and age at diagnosis) also has not been systematically reviewed nor quantified.

The objective of this study is to review all population-based studies up to May, 2002 systematically; to provide quantitative summary estimates of the familial clustering of prostate cancer with emphasis on the degree of relatedness, the relationship of the family member, the number of affected family members and the age at diagnosis; and to evaluate changes in summary estimates due to differences in populations and study designs.

Methods

Search strategy

Publications were identified by the principal investigator through computerized Medline, Embase, Cancerlit and Current Contents searches for population-based studies published until May 2002 with no language restriction. The keywords used were a combination of prostat*, cancer, carcinoma, famil*, father, and brother. Furthermore, references cited in published original and review papers were examined until no further study was identified. For inclusion in this analysis, the papers had to describe a prospective cohort study, a case-control study or a cross-sectional study comparing prostate cancer rates in relatives of patients with population rates providing sufficient information to estimate a recurrence risk ratio (denoted λ) and the associated standard error of incident primary prostate cancer comparing men with and without family member with this disease.

In compiling the database, a distinction was drawn between an article and a study. A study comprises all the analyses of a given group of research subjects. These analyses may be described in more than one article. When the same study population was referred to in more than one article, they were considered as part of a single study. When different results pertaining to the research subjects of a single study were published in more than one article, all such articles were included, but the data were combined to reflect the fact that only one sample of subjects was involved.

Qualitative data extraction

Three blinded reviewers extracted both qualitative and quantitative information from each paper. The original papers were blinded for authors, affiliations, journal name, publication year, and acknowledgements. We independently assessed the following qualitative items: general information (i.e., geographic area, study design), population characteristics (i.e., population size, ethnic label), patient characteristics (i.e., number, histological confirmation, mean age at diagnosis) and the

assessment method of family history. When continuous data were presented across different subgroups, we calculated a weighted mean using the median of each subgroup weighted by the frequency of observations in these strata. When disagreement existed on an item, it was discussed until a consensus was reached.

Quantitative data extraction

We extracted quantitative data allowing us to calculate λ's -estimated by the relative risk in prospective studies and the odds ratio in case-control studies- and corresponding standard errors to estimate the association between prostate cancer risk and family history of prostate cancer among father (λ_f), any brothers (λ_s), any first-degree family members (i.e., father, brother or son, λ_1), one first-degree family member, more than one first-degree family members, any first-degree family members younger than 65 years, any first-degree family members older than 65 years, any first-degree family members of which the proband was diagnosed before the age of 65 years, any first-degree family members of which the proband was diagnosed after the age 65 years and any second-degree family members (i.e., grand father or uncle, λ_2). When the reported λ_1's within a study were stratified for age or other strata, we calculated a within study pooled λ_1 using fixed-effect pooling within age strata. When an age category covered the age 65 years, the corresponding λ_1 was used in the calculation of both estimates (before and after the age of 65 years) using 50% of its weight in each estimate. When the degree of family history was not reported, we assumed this to be first-degree[5,17,20,25]. Preferably adjusted λ's were extracted. When adjusted λ's could not be calculated, we constructed two-way contingency tables, based on exposure frequency distributions, to calculate the unadjusted λ's and corresponding standard errors. The standard error for the unadjusted λ's was calculated by the method of Woolf[45]. Papers reporting ethnically stratified λ's were considered as separate studies so that the ethnic label of a study population could be incorporated as a covariate in meta regression analysis to explore potential sources of heterogeneity.

Statistical Analysis

To detect publication or related biases, we explored heterogeneity in funnel plots, i.e., plots of effect estimates against their estimated precision (reciprocal of the variance). We examined funnel plot asymmetry visually and measured the degree of asymmetry by using Egger's unweighted regression asymmetry test[46]. Standard meta-analytic procedures assume that results within a given analysis are independent. Our sorting of articles into their respective studies ensured that, for any given analysis of family history and prostate cancer, all of the summarized recurrence risk ratios would be based on independent samples. We estimated the summary odds ratios and corresponding 95% confidence intervals (CIs) with random effects meta regression analysis by using the Stata statistical software[47]. The between-study variance was estimated by a non-iterative procedure using a method of moments estimator. To explore reasons for the observed heterogeneity, we performed sensitivity analyses on the study characteristics and tested their influence on the pooled effect estimates. The regression model relates the risk of prostate cancer to the study-level covariates, assuming a normal distribution for the residual errors with both a within-study and an additive between-studies component.

Results

Study Characteristics

The search strategy revealed 44 articles reporting population-based studies on family history and prostate cancer[5-36,48-59]. 12 articles were excluded because prostate cancer mortality was investigated in stead of prostate cancer incidence (n=2)[48,49], no sufficient data could be extracted (n=6)[50-55] or different study designs were used (n=4)[56-59]. Eight articles were combined in the analysis because the same study was published twice (table 1)[9,10,12,14,16,20,29,36]. The 32 articles included[5-36] described five prospective cohort studies in which family history of prostate cancer was assessed *before* diagnosis[5,7,23,24,26], 20 retrospective case-control studies in which family history of prostate cancer was assessed *after* diagnosis[6,8-10,13,15-22,25,27-34,36] and three cross-sectional studies[11,12,14,35] comprising a total of 13,934 patients. Almost all studies were published in English except for one Italian[22] and one Spanish[25] article that were translated to English for data extraction by native-speaking colleagues. All studies identified were performed in Western countries; 22 studies[5,7-11,13,15-21,23,24,27-34,36] were performed in the United States of America or Canada and six studies[6,12,14,22,25,26,35] were performed in Europe. Most studies investigated the association between family history and prostate cancer risk within Caucasian populations[5-12,14-18,21,24,26-30,32-35], although five studies were performed within mixed populations[13,19,20,23,31,36]. The two non-English articles did not provide specific information on ethnic labels but these populations were assumed to have investigated Italian[22] and Spanish[25] populations, respectively. Nine studies[5-7,22,23,26,27,32,34] used questionnaires to assess family history of prostate cancer among family members, whereas 15 studies[8-10,13,15-21,24,28-31,33,36] used interviewing techniques. Three studies[11,12,14,25,35] consulted registries to retrieve information on family history. 18 studies[5,7-10,13,15,17-22,25-28,30,32,36]reported that the identified prostate cancer patients were histological confirmed, although other studies[6,11,12,14,16,23,24,29,31,33-35] could not confirm this. The mean age at diagnosis of the patients across all studies is 66.7 years (sd=4.3) ranging from 56.6 to 74.5 years (table 1).

Publication bias

We could not identify heterogeneity in funnel plots, neither visually (figure 1) nor in terms of statistical significance (*P* values = 1.00, 0.93, 0.21 and 0.62 for father, brother, first and second-degree family members, respectively).

Summary recurrence risk ratios

Almost all studies provided information on the association between family history of prostate cancer among first-degree family member and prostate cancer risk[5-7,9-29,31-33,35,36] (figure 2). Random effect pooling revealed a summary recurrence risk ratio (denoted $S\lambda_1$) of 2.46 (95%CI 2.14 – 2.82). The risk of prostate cancer appeared to be higher for men with an affected brother ($s\lambda_b$: 3.28, 95%CI: 2.84-3.78)[6-10,13,16,18,21,23,24,26,27,29-31,34] than for men with an affected father ($S\lambda_f$: 2.18, 95%CI: 1.89-2.51)[6-10,12-16,18,21,23,24,26,27,29,31,33,34]. Whereas the recurrence risk ratio for men with second-degree relatives with prostate cancer was only slightly elevated ($S\lambda_2$: 1.68, 95%CI: 1.07-2.64)[16,18,24,27,29,31] (figure 2). The risk of prostate cancer for first-degree family members rose with increasing number of affected relatives from 2.43 (95%CI: 2.04-2.89) for men having one first-degree family member with prostate cancer[9,10,16,19,21,29,31] to 3.99 (95%CI: 3.11-5.11) when two or more family members were affected[9,10,16,19,21,29,31,34]. The summary recurrence risk ratio decreased with increasing age of first-degree family members and the proband's age of diagnosis. $S\lambda_1$ was 3.34 (95%CI: 2.64-4.23) for family members younger than 65 years[6,12-14,16,21,29] and 2.35 (95%CI: 2.05-2.70) for older family members[6,12-14,16,21,29]. Furthermore, $S\lambda_1$ was 2.47 (95%CI: 1.71-3.55) for first-degree family members of which the proband was diagnosed before the age of 65 years[12,14,21,31] and 1.72 (95%CI: 1.41-2.10) for any first-degree family members of which the proband was diagnosed after the age 65 years[12,14,21,31].

Sensitivity analysis

We further examined the recurrence risk ratio for first-degree family members by study design, histological confirmation of patients, ethnic label of the study populations, and family history assessment technique to explore their influence on the outcome estimates (figure 3). Most subset specific $S\lambda_1$'s did not differ substantially, although it appeared that the $S\lambda_1$ for cohort studies was somewhat lower than for case-control studies and that the $S\lambda_1$ for studies investigating Caucasian populations was slightly lower than for studies investigating other populations, although these differences were not statistically significant ($p_{cohort}=0.38$, $p_{caucasian}=0.07$) (figure 3). Sensitivity analysis on the study aggregated mean age at diagnosis did not reveal a substantial difference in the risk estimates.

Discussion

The association between family history and prostate cancer risk has been extensively investigated in 32 population-based studies. These studies can be considered as the best available evidence to estimate empiric risk for men with a family history of prostate cancer. The findings suggest a substantially increased prostate cancer risk for family members of a patient. The nature of this familial clustering is such that the recurrence risk rises with decreasing age at diagnosis of the patient and the age of other affected family members, with increasing genetic relatedness of the affected relative and with an increase in the number of individuals affected within the family. We observed a higher risk of prostate cancer in individuals with history of disease in a brother compared to those with history of disease in a father.

The studies included have been conducted in several geographical regions by investigators using a variety of methodological and analytical techniques. Because of potential heterogeneity in populations, designs, and analyses of various studies, we assumed that the true effects being estimated would vary between the studies in addition to the usual sampling variation in the estimates (within studies). To account for both sources of variation, we used random effects meta regression analysis to combine the results from the primary studies[60]. The random effect approach provides some allowance for heterogeneity in studies beyond sampling error.

The results from sensitivity analyses suggested that the recurrence risk ratios were consistent across studies that differed in histological confirmation of patients, ethnic label of the study populations, and family history assessment techniques. It appeared that the summary estimates of case-control studies were somewhat higher than for prospective studies, although not statistically significant. This contrast might also be a consequence of differential recall bias in case-control studies because patients with prostate cancer are possibly more sensitised toward recalling affected family members

than non-cases. Also, the recurrence risk for Caucasians was not significantly different than for other populations. This finding might be explained by the fact that the prevalence of mutant alleles that predispose to familial or hereditary prostate cancer does not differ among populations.

We did not attempt to uncover unpublished observations and excluded studies that did not meet the predetermined criteria. Publication bias might arise by excluding these studies. However, we could not identify funnel plot heterogeneity in our meta-analysis, either visually or in terms of statistical significance.

Family size might have influenced the effect estimates for affected brothers, since the probability of having an affected brother is dependent on the number of brothers of a proband. Unfortunately, we could not allow for family size in this meta-analysis, because the original studies did not report on this sufficiently. We expect this, however, to be non-differential misclassification since differences in family size will probably be the same for cases and controls.

Familial aggregations of prostate cancer found in these epidemiologic studies cannot serve to identify genetic liability in the absence of specific genetic tests. Such familial clustering may be due not only to genetic risk factors for disease, but also to common exposure of relatives to environmental carcinogens[12,41]. There are features of this clustering, however, that may suggest a genetic component. The genetic contribution to disease of complex origin such as cancer is often most salient in families of patients of early-onset. Therefore, one feature of an inherited form of prostate cancer is the increased clustering of prostate cancer in families of patients with early onset as is shown in this meta-analysis. Furthermore, the observation of a higher recurrence risk for family members with a brother with prostate cancer compared to those with an affected father are consistent with a recessive, or X-linked genetic component to prostate cancer susceptibility. The observation that the recurrence risk ratio for first degree family members is higher than for second

degree family members is not consistent with a recessive mode of inheritance. It is possible, nevertheless, that the environment shared by brothers is more similar than that shared by fathers and sons.

Twin studies are more suitable to distinguish shared environment and genetic factors. The National Academy of Sciences Twin Cohort, comprising nearly 16,000 male veteran twins revealed a monozygotic concordance for prostate cancer of 27.1% compared with 7.1% for dizygotic twins, giving strong evidence for the influence of genetic susceptibility to prostate cancer in which multiple loci might be involved. The authors estimated the narrow sense heritability of liability to be 57%[61]. Two Swedish twin registries linked to the Swedish Cancer Registry, identifying cases of cancer diagnosed from 1959 through 1992 in twins born in the period from 1886 confirmed these findings[62].

Segregation analyses also support a genetic susceptibility to prostate cancer[57]. Highly penetrant susceptibility genes with autosomal dominant transmission may account for about 9 percent of all prostate cancer cases with penetrances of 88-89% by 85 years[39,58]. This had led to the development of "Hopkins Criteria" for hereditary, high-risk prostate cancer families in which there are either 1) prostate cancer in three or more first-degree relatives, 2) prostate cancer in three successive generations of either the maternal or paternal lineages, or 3) a cluster of two relatives affected at age <55 years. Linkage analysis in such families has suggested the existence of susceptibility genes on chromosomes 1p36, 1q24-25, 1q42.2-q43, 20q13 and Xq27-q28, although age-related penetrances associated with mutations in any of these loci have not been reported[63]. Evidence for RNaseL as the HPC1 gene as the HPC1 locus on chromosome 1q24-q25 has recently been presented[64]. It has been inferred that such high-risk genes might function as tumour suppressors[38].

Heritable prostate cancer with fewer affected members and, thus, lower recurrence risk ratios, may result from polymorphisms in other genes. Among the candidate genes are those associated with androgen production or response, including the androgen receptor (AR), steroid 5-α-reductase type II (SRD5A2), CYP17, aromatase (CYP19), and 3-β-hydroxysteroid dehydrogenase type II genes[65-71]. The prevalence of high-risk alleles of some of these genes is also agreement with the risk of prostate cancer by ethnic group[69,72]. However, in one study, polymorphisms in the AR gene did not appear to play a major role in familial prostate cancer[73]. Thus, it is not yet clear about which genetic tests to offer to men who may have had a brother or father affected with prostate cancer at age 55.

Nonetheless, the physician or genetic counsellor can use this information about the risks of prostate cancer associated with positive family history to counsel men, currently unaffected with disease. As estimated from this meta-analysis, the empiric risk for the first-degree relative of a man affected with prostate cancer is more than twofold compared to the risk of patients with no family history of this disease. This recurrence risk ratio can be multiplied with the lifetime risk of prostate cancer in the general population to estimate the absolute risk of prostate cancer for an individual with an affected family member. Epidemiological studies to date have revealed no other risk factor as consistently and strongly associated with the development of prostate cancer as that of a positive family history of disease. Men with a positive family history of disease constitute an easily identifiable high risk group who could benefit from PSA screening at an earlier age and at shorter intervals compared to the general male population[39,41]. When elevated, these men will be candidates for diagnostic work-up to determine whether, in fact, they are affected with prostate cancer[74].

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TABLE 1. Study characteristics of published population-based studies concerning family history of prostate cancer and prostate cancer risk.

Ref.	Country	Design	Ethnic label	Assessment	Patient Characteristics		
					Number	Histological Confirmation	Mean age (years)
[5]	Canada	Prospective study	Caucasian	Questionnaire	902	Yes	66.3[x]
[6]	Sweden	Case-control study[p/h]	Caucasian	Questionnaire	356		72.1
[7]	USA	Prospective study	Caucasian[99%]	Questionnaire	101	Yes	73.8[x]
[8]	USA	Case-control study[p]	Caucasian[67%]	Interview[q]	382	Yes	45+
[9,10]	Canada	Case-control study[p]	Caucasian	Interview	640	Yes	69.2[x]
[11]	USA	Cross-sectional study	Caucasian	Registry	1376		
[13]	USA	Case-control study[p]	Mixed[b,c]	Interview	972	Yes	60.7[x]
[12,14]	Sweden	Cross-sectional study	Caucasian	Registry	1035	No	
[15]	USA	Case-control study[n]	Caucasian	Interview	216	Yes	56.6[x]
[17]	USA	Case-control study[r]	Caucasian[97%]	Interview	57	Yes	64.7[x]
[18]	USA	Case-control study[s]	Caucasian[95%]	Interview	1084	Yes	64.7
[19]	USA	Case-control study[p]	Mixed	Interview	452	Yes	71.3[x]
[20,36]	USA	Case-control study[h]	Mixed	Interview[q]	210	Yes	69
[21]	USA	Case-control study[p]	Caucasian	Interview	563	Yes	65
[22]	Italy	Case-control study[h]	Italian	Questionnaire[m]	75	Yes	
[23]	USA	Prospective study	Mixed[a,b,c,d,]	Questionnaire	1486		62.6[x]
[24]	Canada	Prospective study	Caucasian	Interview	264		66.3
[25]	Spain	Case-control study[h]	Hispanic		90	Yes	74.5
[26]	Netherlands	Prospective study	Caucasian	Questionnaire	704	Yes	63.9[x]
[27]	USA	Case-control study[h]	Caucasian[95%]	Questionnaire	385	Yes	66.2
[28]	Canada	Case-control study[h]	Caucasian	Interview	39	Yes	69
[16,29]	USA	Case-control study[s]	Caucasian[96%]	Interview	691		62.6
[30]	USA	Case-control study[p]	Caucacian	Interview	358	Yes	67.5[x]
[31]	USA / Canada	Case-control study[p]	Mixed[a,b,c]	Interview	1500		70.9[x]
[32]	USA	Case-control study[p]	Caucasian[95%]	Questionnaire	175	Yes	64.0
[33]	USA	Case-control study[h,n]	Caucasian	Interview	36		
[34]	USA	Case-control study[h]	Caucasian[98%]	Questionnaire	1271		67.6
[35]	Sweden	Cross-sectional study	Caucasian	Registry	16[f]		72

[a]Separate effect estimates available for Asian study participants
[b]Separate effect estimates available for Black study participants
[c]Separate effect estimates available for Caucasian study participants
[d]Separate effect estimates available for Hispanic study participants
[f]Only patients with family history of prostate cancer were reported
[h]Controls were recruited from Hospitals
[m]Family history was assessed using questionnaires among controles and Medical records among patients
[n]Controls were recruited from general population using Neighbours
[p]Controls were recruited from the general Population
[r]Cohort study in which family history was measured Retrospectively
[s]Controls were recruited from Spouses
[q]Structured Interview using Questionnaire
[x]Mean Age was not given, but recalculated from the original report

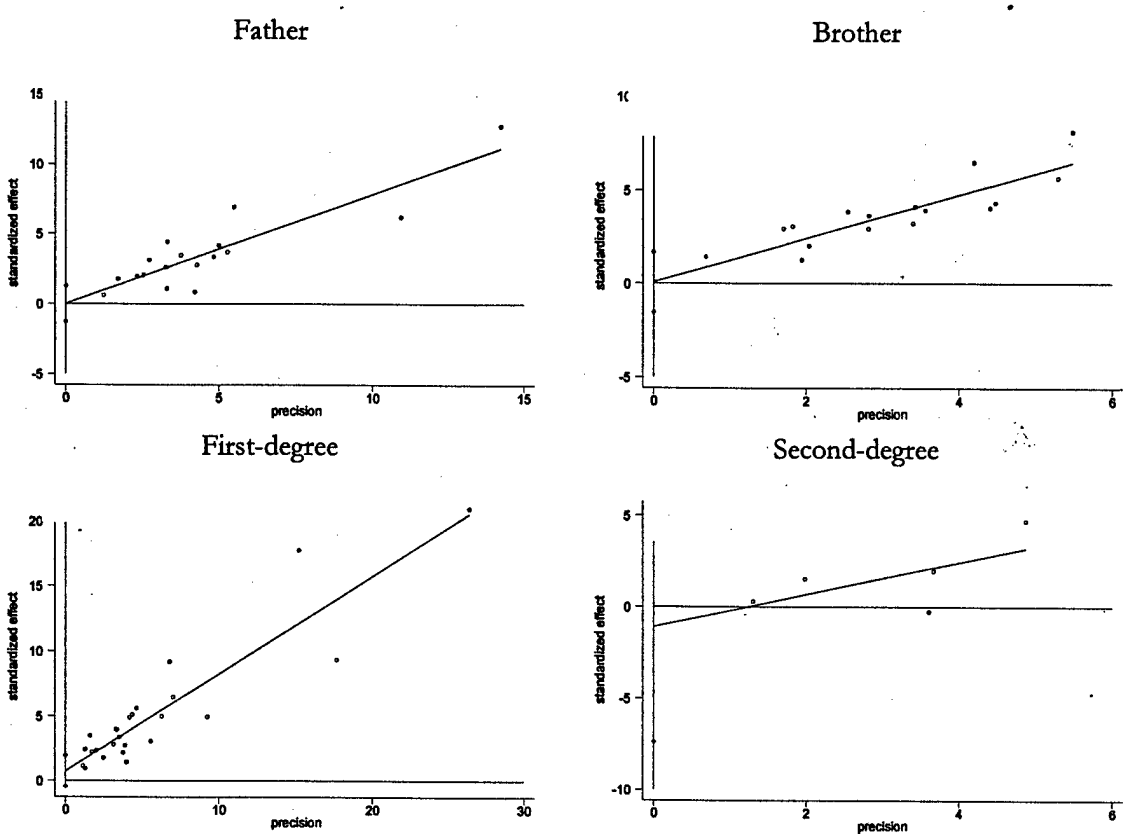

FIGURE 1: Publication bias plot for family members with an affected father, brother or affected first or second-degree relatives, respectively.

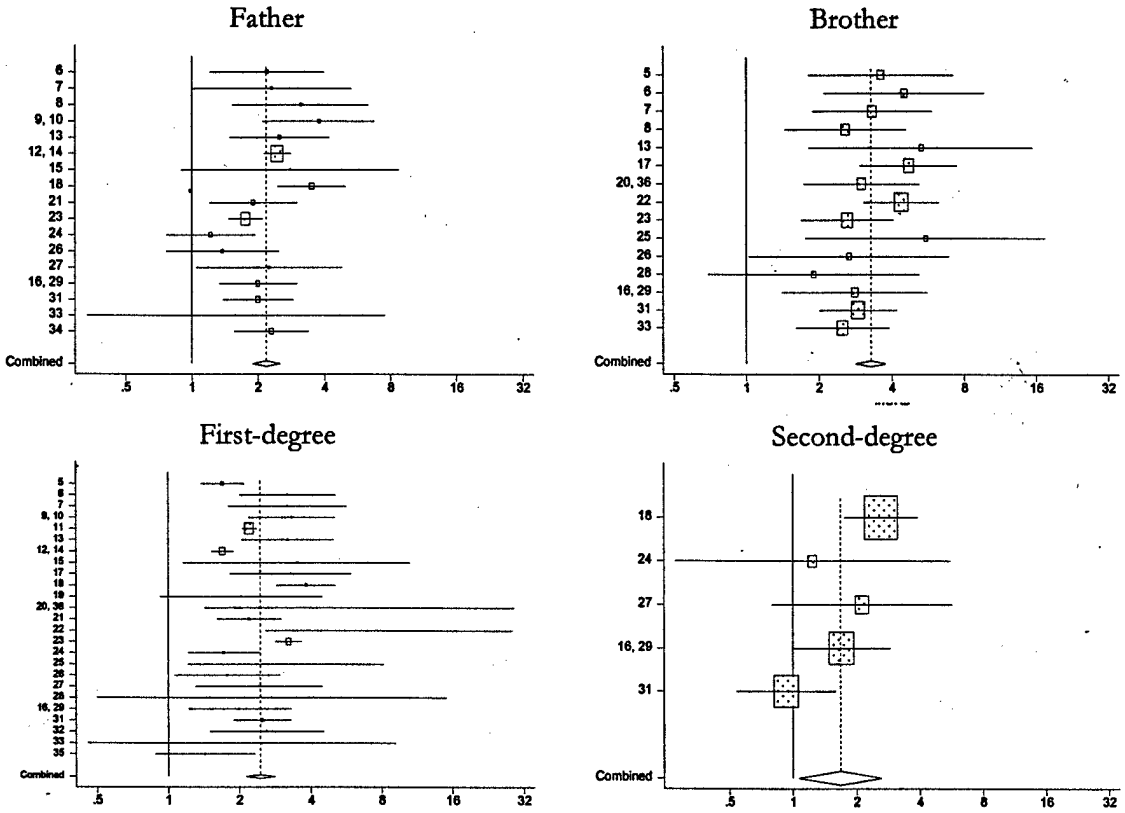

Figure 2: Study specific and summary recurrence risk ratios for family members with an affected father, brother or affected first or second-degree relatives. Dashed and solid reference lines indicate summary recurrence risk ratio and no effect, respectively.

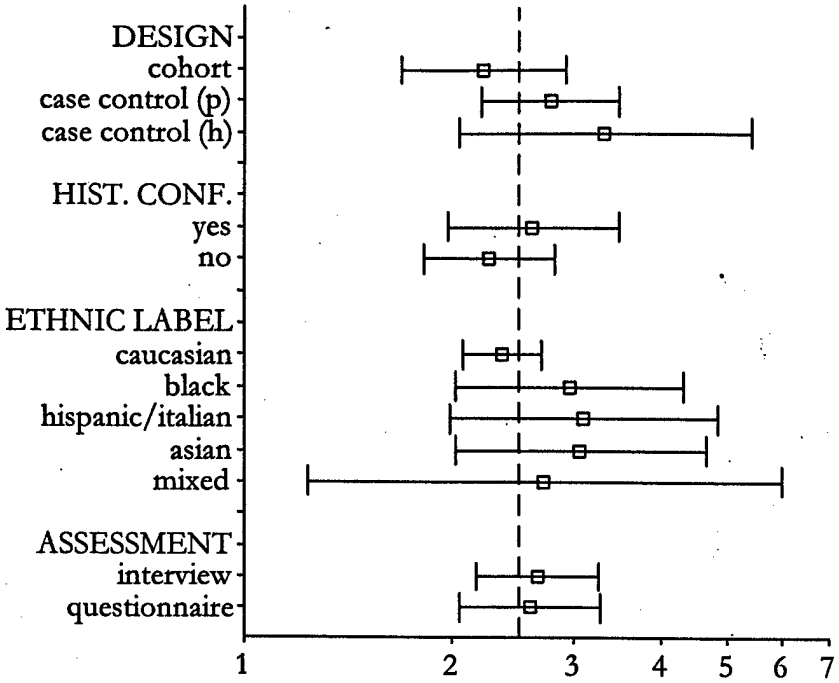

Figure 3: Summary recurrence risk ratios for family members with an affected father, brother or affected first or second-degree relatives by study design (cohort study, population-based case-control study, hospital based case-control study), histological confirmation of prostate cancer among cases (yes, no), ethnic label (Caucasian, black, Hispanic/Italian, Asian, mixed), and family history assessment technique (interview, questionnaire). Dashed and solid reference lines indicate summary recurrence risk ratio and no effect, respectively.

8/19/02

Genetic counseling for prostate cancer risk

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Keywords:

Prostate cancer
Risk assessment
Genetic counseling
Screening

Introduction

Prostate cancer is the most commonly diagnosed cancer of men and the second leading cause of cancer deaths among men in the United States. In 2002, it is expected that 189,000 men will be diagnosed and that 30,000 men will die from this disease in the United States (1). With the advent of improved screening methods using prostate specific antigen (PSA) and digital rectal exam (DRE), emphasis has been place on identifying prostate cancer in its earliest stages when cure may be most likely. Certain men are at increased risk for developing prostate cancer based on their family history and ethnicity. Here, we review those risks and how the clinical geneticist, genetic counselor, or other health care practitioner might incorporate the information when counseling patients.

Who is genetically at risk?

A positive family history is a significant risk factor for developing prostate cancer. This observation was derived from studies that demonstrated familial clustering. Twin studies showed that this risk is based in part from a shared genetic predisposition. Utilizing twin registries from the Department of Veterans Affairs, the concordance rate for prostate cancer was substantially greater among monozygotic (27.1%) than among dizygotic twin pairs (7.1%) (2) From this study, genetic influences were extrapolated to account for approximately 57% of the variance in twin liability. Similar results were observed from a study of the twin registries of Denmark, Sweden and Finland, where the heritability of prostate cancer was calculated to be 42% (3).

The magnitude of prostate cancer risk associated with a positive family history of this disease was derived from epidemiologic studies. Both the number of affected male relatives and their age at diagnosis contribute to the risk. In some families, the pattern of inheritance simulates a Mendelian dominant trait. This condition, termed, "hereditary prostate cancer" is based on the following criteria: a cluster of three or more first-degree relatives with prostate cancer, or prostate cancer in each of three generations in the paternal or maternal lineage, or two or more first or second-degree relatives with prostate cancer under the age of 55 (4, 5). Yet, having as few as one affected relative may contribute to the risk. This condition of one or two affected relatives is termed, "familial prostate cancer."

Ethnicity also contributes to prostate cancer risk. African-American men have long been known to have the highest rates of prostate cancer in the world, whereas native Japanese and Chinese men have lowest known rates (1, 6, 7). For example, the incidence age-adjusted rates in the combined 11 SEER registries expressed as cases per 100,000 population are 159 for Caucasians, 257 for African-Americans, and 101 for Asians (7). This difference among ethnic groups appears to be explained on the basis of variation in the incidence of clinical disease, rather than latent prostate cancer.

What is the risk of developing prostate cancer?

A man's risk for developing prostate cancer increases with the number of affected male relatives (8-20). These risks have been compiled in a recent meta-analysis of the empiric risk of prostate cancer. Here, they have been adapted to provide ranges of cumulative risks by age for

family members (Table) (21). A man with one first-degree relative is twice as likely as men in the general population to develop prostate cancer. Moreover, if his relatives develop prostate cancer at an earlier age, the risk is increased further. With two or more first-degree relatives affected at an early age (less than 65), the risk is increased four-fold.

Table: Cumulative Risk for Developing Prostate Cancer by Age, Family History and Ethnicity

White men

Relationship	**Relative Risk**	**Cumulative Risk in Percent by Age (with 95% CI)**			
		40	50	60	70
No family history	1	0.005	0.162	2.04	7.5
One first-degree relative	2.43 (2.04, 2.89)	0.012 (0.010, 0.014)	0.394 (0.330, 0.468)	4.95 (4.16, 5.89)	18.22 (15.30, 21.68)
Family member diagnosed <65	3.34 (2.64, 4.23)	0.017 (0.013, 0.021)	0.541 (0.428, 0.685)	6.81 (5.39, 8.63)	25.05 (19.80, 31.73)
Family member diagnosed >=65	2.35 (2.05, 2.70)	0.012 (0.010, 0.014)	0.381 (0.332, 0.437)	4.79 (4.18, 5.51)	17.63 (15.38, 20.25)
Two or more first-degree relatives	3.99 (3.11, 5.11)	0.020 (0.016, 0.026)	0.646 (0.504, 0.828)	8.14 (6.34, 10.42)	29.93 (23.33, 38.33)
Second degree relative	1.68 (1.07, 2.64)	0.008 (0.005, 0.013)	0.272 (0.173, 0.428)	3.43 (2.18, 5.39)	12.60 (8.03, 19.80)

Black men

Relationship	**Relative Risk**	**Cumulative Risk (Percent)**			
		40	50	60	70
No family history	1	0.009	0.417	3.589	10.549
One first-degree relative	2.43 (2.14, 2.82)	0.022 (0.019, 0.025)	1.01 (0.89, 1.18)	8.72 (7.68, 10.12)	25.63 (22.57, 29.75)
Family member diagnosed <65	3.34 (2.63, 4.23)	0.030 (0.024, 0.038)	1.39 (1.10, 1.76)	11.99 (9.44, 15.18)	35.23 (27.74, 44.62)
Family member diagnosed >=65	2.35 (2.05, 2.70)	0.021 (0.019, 0.024)	0.98 (0.86, 1.13)	8.43 (7.36, 9.69)	24.79 (21.63, 28.48)
Two or more first-degree relatives	3.99 (3.11, 5.11)	0.036 (0.028, 0.046)	1.66 (1.30, 2.13)	14.32 (11.16, 18.34)	42.09 (32.81, 53.91)
Second degree relative	1.68 (1.07, 2.64)	0.015 (0.010, 0.024)	0.70 (0.45, 1.10)	6.03 (3.84, 9.47)	17.72 (11.29, 27.85)

For genetic counseling purposes, we have multiplied these relative risks by age-related cumulative risks in the Surveillance, Epidemiology, and End Result (SEER) Program of the National Cancer Institute to derive cumulative risks for men with different family histories. (7). The cumulative risks for men with two affected first-degree relatives simulates an autosomal dominant trait (4, 22). For Caucasian men with two affected first-degree relatives, the cumulative risks at ages 60 and 70 are greater than those that were observed in a Swedish study

that was based on a national registry (10). This may be explained on the basis of greater baseline risks among the Swedes, rather than greater familial risks.

For African-American men, the risks of developing prostate cancer based on ethnicity alone are 40-80% greater than for Caucasian men. Although the baseline risks for developing prostate cancer are different, the familial risks do not vary with ethnicity (21). This is reflected in the risk figures presented in the table. The net effect of family history is to make the risks for younger men with a positive family history comparable to that for older men without a family history. The net effect of ethnicity is to make the risks for younger African-American men comparable to that for older Caucasian men. These figures suggest that screening for men at higher risk based on family history or ethnicity should start 5-10 years earlier than for men with average risk.

Are heritable or familial prostate cancer different than sporadic prostate cancer?

If heritable or familial prostate cancer were more aggressive, then patients with a positive family history might require different treatment from patients with sporadic disease. Both familial and hereditary prostate cancer are diagnosed approximately 6 to 7 years earlier than the sporadic form of the disease (23, 24). Natural history studies suggest that the disease in these patients for the most part does not differ in clinical presentation, response to treatment or survival.

Several studies showed that there were no statistical differences in symptoms, pathologic stage, Gleason scores, margins, or in PSA recurrence in prostate cancers that are characterized as

hereditary, familial or early-onset (23-28). However, the tumors tend to be well-differentiated and low-grade, possibly explained by an increased awareness of the disease in families at risk. The authors of these studies concluded that no difference in treatment is justified exclusively on the basis of family history. These observations apply not only to surgically-treated prostate cancer, but also to prostate cancer treated with external-beam radiation, for which no difference in response was observed between men with and without a family history of prostate cancer (29). One study observed an increased rate of higher-grade tumors and advanced-stage disease in men with hereditary prostate cancer linked to a specific gene, suggesting that subgroups may exist (30).

In contrast, African-American men with prostate cancer tend to have a more virulent form of the disease compared to Asian, Caucasian and Hispanic men. This difference has been observed at clinical presentation. In a multi-institutional retrospective analysis of over 1000 men with prostate cancer, black men were significantly younger than their white counterparts at diagnosis (65.2 vs. 67.4 years), had higher stage of disease, higher Gleason scores, and higher mean PSAs (31). In a prospective analysis of screening for prostate cancer by PSA and DRE, black men had a significantly higher percentage of positive biopsies when matched with their white counterparts for PSA level (32). Thus, the positive predictive value of a suspicious DRE in black men was much higher than in white men. Even when controlling for PSA and age, black race remained a significant predictor of prostate cancer. A study of 651 consecutive men who underwent radical prostatectomy at a single institution showed that at a PSA level of 4.1 to 7.9, black men had a statistically lower percentage of organ confined disease compared to white men (63.5% vs. 48.9 %, respectively) (33). Conversely, in a retrospective review of men with

normal PSA and an abnormal DRE, cancer detection was found to be essentially equivalent between black (21%) and white (18%) men (34).

Prostate cancer among African-American men may be more aggressive not only at presentation, but also respond less favorably to therapy. Two studies from the same investigators showed that race is an independent predictor for recurrence in men with prostate cancer. (33, 35). Yet, another study found that race was not a predictor of failure. The only observed difference was a statistically higher initial PSA level at presentation in African-American men compared to Caucasian men (13.3 vs. 8.6, respectively) (36).

Are the relatives of men with prostate cancer at increased risk for other cancers?

Clustering of prostate and other cancers within families suggests that men with a positive family history of prostate cancer may be at risk for other malignancies. One study from the Utah Population Database showed that first-degree relatives of probands with prostate cancer at moderately increased risk for colon cancer, non-Hodgkin's lymphoma, rectal cancer and brain cancer (37). Among 12 Utah prostate cancer kindreds, an excess of cancers of other types was observed in 7 families: 3 with colorectal cancer, two with non-Hodgkin's lymphoma, and one each with lip and bladder cancer (38). However, there was no increased risk of developing other malignancies. The increased risk for developing central nervous system tumors was observed in another American study of families with hereditary prostate cancer (9). A study of 62 Swedish families with hereditary prostate cancer identified a moderately increased risk for breast, gastric and kidney cancer. A subset of 7 families had two or more relatives affected with these cancers (39). A study of first-degree male relatives of Swedish men with prostate cancer did not identify

increased risk for any tumors other than prostate (19). These findings suggest that either a common environmental exposure is present for families that have multiple cancers, including prostate, and/or that some families have a genetic predisposition resulting in a cancer family syndrome.

A recent genetic linkage study provided evidence in support of a prostate-brain cancer family syndrome. This study of 12 families with prostate cancer and a relative with a primary brain cancer demonstrated linkage at chromosome 1p36 (LOD score 3.65 at theta = 0 for D1S407) (40). The aggregation of prostate, colon and breast cancer might constitute another cancer family syndrome, but this is unlikely to arise from inheritance of mutations in the BRCA 1 or 2 genes (41-46).

What is the role of genetic testing for men at increased risk for prostate cancer?

Linkage analysis of men from high-risk families has led to the identification of multiple susceptibility loci at 1q24-q25, 1q42.2-q43, 1p36, 17p, 20q13, and Xq27-q28 (40, 47-51). Within some populations, the high-risk loci might account for a significant proportion of cases. For example, the HPCX locus on the X chromosome has been calculated to account for 45% of hereditary prostate cancer cases in Finland (52). This appears to be the exception, rather than the rule, because a major problem with the linkage studies has been the difficulty of replicating findings across populations with hereditary prostate cancer (53).

This feature of low attributable risk has been observed for the susceptibility genes that have been cloned, including the HPC2/ELAC gene at 17p and the HPC1/RNASEL gene at 1q24-q25 (50, 54). In the original study, a frameshift mutation and a non-conservative missense mutation in HPC2/ELAC2 each segregated in a high-risk family (50). One other truncating mutation was found to segregate in two of three affected members in a family with prostate cancer (55). The missense mutation in the HPC2/ELAC gene, Ala541Thr, showed an association with prostate cancer in some case-control studies, but not in others (55-59). None of these studies showed that the polymorphism segregated with familial cases. When tested as an adjunct to PSA screening, polymorphism testing did not improve the prediction of who was affected with prostate cancer (60).

Truncating mutations in RNASEL were observed in two families with hereditary prostate cancer (54). Microdissected tumors showed loss of heterozygosity and decreased protein expression for this gene, suggesting that it might function as a tumor suppressor. In a set of Finnish families with hereditary prostate cancer, a truncating mutation E265X, was observed in 4.3% of affected men (54). This mutation was associated with an odds ratio of 4.56 and a mean age of onset that was 11 years earlier than affected non-carrier members from the same families. No other mutations were found in this gene that could account for the risks in the remainder of the Finnish prostate cancer families. Homozygosity for the more common Arg allele compared to the Gln allele at codon 462 increased the risk for familial, compared to sporadic, prostate cancer (61). Homozygosity for the Gln allele was associated with earlier-onset, but milder disease. Among Ashkenazi Jews, the frameshifitng 4712delAAAG mutation was observed among 6.9% of patients with prostate cancer compared to 2.4% of age-matched controls and

among 28.6% of those with a positive family history (62). This allele was observed to be in linkage disequilibrium with the closely linked markers D1S2182 and D1S158, and thus, to be a founder mutation. The numbers of subjects in this study was small for drawing statistically meaningful conclusions. Overall, mutations in RNASEL do not appear to be a major cause for hereditary prostate cancer, but may be important in some groups.

Length polymorphisms in CAG trinucleotide repeat the androgen receptor are associated with increased risk for developing prostate cancer. Shorter polymorphisms are associated with approximately 2-fold increased risk (63-66). The prevalence of shorter, high-risk alleles is in agreement with the risk of prostate cancer by ethnic group (67). Polymorphisms in the AR gene do not segregate with the familial risk (68). Thus, it is not yet clear about which genetic tests to offer to men who may have had a brother or father affected with prostate cancer at age 55.

What is the role of screening for men at increased risk for prostate cancer?

Screening for prostate cancer is endorsed by some, but not other, professional groups. The American Urological Association recommends that PSA and DRE screening start at age 50 in the general population and at age 40 for men in high-risk groups (men with a positive family history and African-American men) (69). The American Cancer Society similarly recommends that screening starts at age 50 for men in the general population, at 45 for African-American men and for men with one affected first-degree relative, and at 40 for men at higher risk (70). However, the American College of Physicians and the American College of Preventative Medicine recommend against the use of routine screening (71, 72). Those who are proponents of screening argue that since the widespread advent of PSA testing, there has been a migration to

lower stages of disease at diagnosis, which would ultimately lead to an overall reduced cause-specific mortality rate. Though the data are still somewhat premature, there are early reports from on-going prospective studies demonstrating a decreased mortality secondary to prostate cancer screening. During an eight-year period in Quebec, the death rates from prostate cancer were statistically lower among those men who were screened (15 and 48.7 per 100,000 man-years in the screened and unscreened groups, respectively) (73). A similar decrease in mortality rates was observed among Austrian men screened for prostate cancer (74).

Those who argue against prostate cancer screening believe screening leads to an overdetection of incidental, non-significant cancers. Furthermore, they argue that much of the anecdotal data demonstrating a survival benefit among those screened for prostate cancer is secondary to selection of men with early-stage, milder disease. There was also concern that the positive predictive value of screening with PSA alone was only ~33%, but this data was based on urologists' performing 6 biopsies, rather than the current 12 (75). However, when combined with an abnormal DRE, this PPV increased to 40-60% (76, 77).

Ultimately, the validity of the argument supporting prostate cancer screening will be a decrease in cause-specific death rates. On-going screening trials are currently evaluating this question. The answer should be known within a decade when the European Randomized Study of Screening for Prostate Cancer and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute are completed (78, 79).

How do men view genetic testing for prostate cancer risk?

In 2002, health care providers can identify those men at an increased risk for developing prostate cancer during their lifetimes. These men are candidates for increased surveillance using screening. However, testing is not necessarily a benign procedure, and there are inherent emotional and physical risks involved with diagnosing and treating prostate cancer.

The understanding of American men and their perceptions about screening have been assessed in several studies. In one study of 342 men presenting for an annual prostate cancer screening clinic, 90% of those surveyed understood that age is a risk-factor for prostate cancer, but only 47% knew that ethnicity was a risk factor (80). A large percentage (89%) of the men expressed an interest in genetic testing and indicated they would agree to be tested if available. Another survey of first-degree relatives similarly demonstrated that men at risk have poor understandings of the etiologic risk factors for developing prostate cancer (81). A third study surveyed small focus groups specifically evaluating men's beliefs and values about genetic testing (82). Not surprisingly, men expressed various concerns, including their future insurability, their need for other types of screening (e.g., yearly DREs), insurance costs, and follow-up testing if found to be genetically predisposed to hereditary prostate cancer (83).

Conclusion

Genetic counseling of men at increased risk for prostate cancer should include a detailed family history about diagnosis and age of onset of prostate and other cancers in family members. (The latter is useful if more than one cancer syndrome gene is segregating in a family.) From the pedigree analysis, an age-related risk estimate can be provided to gauge when screening for

prostate and possibly other cancers should be offered. Reassurance can be provided that a positive family history does not appear to change the course of the disease, if and when it occurs. For men who come from families with multiple affected members, participation in a research study should be offered with the understanding that a significant LOD score may not be found for that family. It is hoped that with additional research, genetic markers will be identified that predict not only the risk for developing prostate cancer, but also the course of the disease once it occurs. The results of attitudinal surveys suggest a need to improve public health education about prostate cancer risks among men.

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